Case Report

Leflunomide induced fatal dress syndrome

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Leflunomide induced fatal dress syndrome need liver transplantation

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Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe, potentially life-threatening, drug-induced hypersensitivity reaction that involves hematological abnormalities (atypical lymphocytosis, eosinophilia), lymphadenopathy, skin eruption, and internal organ involvement (lung, liver, kidney). The 36-year-old female patient was followed by bloody diarrhea, diffuse skin rashes and hepatitis. She was diagnosed with psoriatic arthritis, and Leflunomide 20 mg was added to the treatment six weeks ago. Upon developing hepatic encephalopathy and deepening the fulminant liver failure during the follow-up, a living donor liver from her son was transplanted on the 4th day of hospitalization. The patient had deceased on the second day after liver transplantation due to multiple organ failures. In the literature, mortality in DRESS syndrome is mostly secondary to hepatic failure. Liver transplantation cannot be effective due to systemic involvement and recurrence in the transplanted liver.

Keywords: Drug reaction; leflunomide; liver transplantation.

Introduction

Drug-induced hypersensitivity syndrome (DIHS), also known as DRESS syndrome, is infrequent but potentially life-threatening. It is characterized by a drug-induced hypersensitivity reaction that involves hematological abnormalities (atypical lymphocytosis, eosinophilia), lymphadenopathy, skin eruption, and internal organ involvement (lung, liver, kidney).[1]

The pathogenesis of DRESS syndrome is not fully understood. Deficiency or defective epoxide hydroxylase enzyme, which detoxifies the metabolites of aromatic amine anticonvulsants, is the most important reason held responsible for its etiology. It is thought that increased reactive metabolites cause an immunological reaction due to insufficient detoxification of the responsible drug. Ethnic predisposition due to some HLA alleles has also been suggested to be effective in DRESS syndrome. In addition, the reactivation of herpes viruses such as Epstein-Barr Virus (EBV), cytomegalovirus (CMV), human herpes virus (HHV) 6, and HHV 7 is thought to trigger the reaction. DRESS syndrome has a prolonged delay (ranging from two to eight weeks) between drug exposure and symptom onset. It frequently relapses despite stopping the drug. It has often been associated with the reactivation of latent infection of Human Herpes Virus 6.[2] Antiepileptic agents (phenobarbital, phenytoin, carbamazepine, lamotrigine), allopurinol, and antibiotics are the most commonly identified causative agents.[2]

Several factors have been implicated in the function of the epoxide hydroxylase enzyme: polymorphisms in the genes that encode the enzyme that metabolizes drugs, such as cytochrome P450 (CYP450) and N-acetyltransferase, decrease the activity of these enzymes leading to the accumulation of these drugs or their active metabolites, thereby stimulating immune responses by interacting with cellular proteins or peptides.[3] Genetic mutations that affect the epoxide hydroxylase enzyme have also been reported to result in the accumulation of toxic metabolites leading to the emergence of immunological responses. The probability of slow metabolism of the CYP450 system results in the accumulation of toxic hydroxylamine, thereby leading to sulfonamide-related hypersensitivity reactions.[4]

Clinical findings usually appear 2–8 weeks after initiating the responsible drug. Symptoms may persist or even worsen despite discontinuation.[2] The spectrum of skin manifestations is very wide. When the clinic of the syndrome is fully developed, fever, lymphadenopathy, hematological disorders, and internal organ involvement may be seen in addition to severe mucocutaneous clumps. Diagnosis of DRESS syndrome is difficult due to different organ involvements and diversity of skin findings. The basic features of rash, fever, and internal organ involvement can imitate many diseases, especially infections.[5]

The mortality risk is approximately 10–20%, so early recognition of DRESS patients is very important.[4] There is no descriptive study other than a few case reports for DRESS syndrome in our country.

In this study, we presented a case who developed DRESS syndrome due to Leflunomide and underwent liver transplantation.

Case Report

A 36-year-old female patient hospitalized with bloody diarrhea, diffuse skin rashes, and hepatitis at an external healthcare center was admitted to our institution due to a progressive increase of INR and worsening liver function tests (LFTs) for a close follow-up in terms of liver transplantation.

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Table 1. Laboratory results

	AST (U/L)	ALT (U/L)	ALP (U/L)	Albumin (g/dL)	Total bilirubin (mg/dL)	LDH (U/L)	Creatinine (mg/dL)	INR	PLT (10^9/L)
1st day	548	568	174	1.7	6.8	1208	0.4	2.2	62
2nd day	1005	791	217	2.1	11.1	2001	0.44	2.3	55
3rd day	1225	1061	250	2.1	13.5	2004	0.5	2.5	37
4th day (Tx day)	575	947	212	2.1	16.1	1269	0.46	2.5	33
Normal values	5–34	0–55	40–150	3.5–5	0.2–1.2	125–243	0.57–1.11	0.8–1.2	150–400

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; INR: International normalized ratio; PLT: Thrombocyte; Tx: Transplantation.

In the physical examination, the patient was conscious, oriented, and cooperative. There was xerosis on the lips, diffuse morbilliform eruptions, and desquamations on the anterior and posterior extremities.

She had a history of psoriatic arthritis and was followed up for ten years. Leflunomide 20 mg orally once a day was added to the treatment six weeks ago. She presented with bloody diarrhea at the 4th week of treatment and reported that skin rashes had appeared. The patient was hospitalized at the infectious disease clinic and then at the dermatological ward. A colonoscopy was performed due to bloody diarrhea. The entire mucosa of the colon was spontaneously fragile, hemorrhagic, and ulcerated. Pulse steroid therapy was initiated, considering clinical manifestations supported an adverse drug reaction. There was a partial reduction in bloody diarrhea and skin rashes after steroid treatment, but progressive deterioration was observed in her LFTs.

Laboratory findings in our institution after the initiation of steroid treatment were as follows: WBC 6.3x10^9/L, PLT 62x10^9/L, eosinophil 0.45x10^9/L, Hb 9.6 g/dL, INR 2.21, creatinine 0.42 mg/dL, total protein 5 g/dL, albumin 1.7 g/dL, ammonia 126 µg/dL, ALT 568 U/L, AST 548 U/L, LDH 1208 U/L, total bilirubin 6.7 mg/dL, and direct bilirubin 5 mg/dL.

HBs Ag, Anti-HCV, Anti-HIV, Anti-HAV IgM, Anti-HEV IgM, EBV IgM, HSV IgM, CMV IgM, and autoimmune hepatitis panel were tested and found negative. Based on liver enzymes, liver injury was classified as a hepatocellular pattern (R=8.9). The results of the laboratory tests were elaborated in Table 1.

Abdominal USG and computerized tomography (CT) tests showed increased liver size, periportal edema, and diffuse decrease in parenchymal density.

Intravenous hydration and supportive treatment were initiated during hospitalization at our clinic. Upon developing hepatic encephalopathy and the development of fulminant liver failure during the follow-up, a living liver donor (from her son) was transplanted to the patient on the 46th day after the initiation of Leflunomide treatment.

Extubation of the patient could not be performed after liver transplantation. A progressive increase in liver function values and INR was observed in the follow-ups. In addition, a decrease in urine output and an increase in creatinine levels were observed. Hypotension and tachycardia continued, and the clinical status of the patient deteriorated significantly. On the second day after liver transplantation, the patient had deceased secondary to multiple organ failure.

Discussion

Leflunomide is an immunomodulatory agent that inhibits the dihydroorotate dehydrogenase enzyme, which is responsible for the *de novo* synthesis of pyrimidine-containing ribonucleotides. Activated T lymphocytes are susceptible to the drug's effect.[4]

Jaundice and hepatomegaly may be present in DRESS syndrome. Routine liver function tests often detect hepatitis. Liver function tests are elevated, generally mild, and transient, but severe impairments in liver functions may be seen. In a comprehensive prospective DRESS syndrome study, visceral organ involvement was 91%, and out of these, 75% had liver involvement.[3]

The first case of Leflunomide-induced DRESS syndrome in the literature was a 40-year-old male patient who had complaints regarding joint pain, and despite prednisolone and methotrexate treatment, complaints could not be resolved. Symptoms were developed on the 20th day of Leflunomide treatment. Followed by drug stops, and after oral prednisolone treatment, clinical improvement was observed.[6]

Gupta et al.[4] followed up on 46 rheumatoid arthritis patients who underwent Leflunomide treatment and detected an increase in liver function tests of 10 patients. There was an improvement in LFT values after discontinuing the drug in two of these cases, decreasing the drug dose to half in five cases and without any drug dose and change in three patients. In most of the patients who developed DRESS syndrome induced by Leflunomide, diarrhea was present, including our case, who also had bloody diarrhea.

''A 60-year-old male patient'' who had used sulfasalazine due to polyarthritis had developed DRESS syndrome secondary to vancomycin and had undergone liver transplantation due to fulminant hepatic failure. Unfortunately, DRESS syndrome re-developed in the transplanted liver and the patient died.[7] In a series by Ichai et al.,[8] consisting of 16 DRESS syndrome cases, 7 patients had clinical deterioration (five patients had liver transplantation, and two patients died). Of the five patients with liver transplantation, three had a recurrence of the disease. In a study of 27 cases with DRESS syndrome, liver involvement was developed in 9 patients, liver transplantation was performed in one patient, and three patients died.[9]

Most of the deaths associated with DRESS syndrome are due to severe hepatitis. Bilirubin elevation, increased aspartate aminotransferase, and hepatic encephalopathy are the most important determinants of mortality.[10] In our case, on the second day of liver transplantation, the patient died due to multiple organ failures.

In the clinical setting, skin rash, liver involvement, fever, hypereosinophilia, and lymphadenopathy should lead to suspicions regarding DRESS syndrome. Moreover, reactivation with HHV-6 and other herpes viruses is an indication of a complex immunopathogenesis. Therefore, the responsible medication should be discontinued

immediately. Supportive precautions, in addition to standard wound care, multidisciplinary approaches, and corticosteroid treatment if necessary, should be started to minimize mortality and morbidity.[2]

In conclusion, due to the wide range of clinical features and the latent period, due to its long duration, there are often delays in the diagnosis of DRESS syndrome.[1,2] The fact that the same group of drugs can be fatal with repeated use makes the early diagnosis of the disease more important. We believe that with the increase in the number of patients diagnosed and followed up and sharing this information, new DRESS cases will be recognized and remembered earlier. Early diagnosis of the disease and discontinuation of the responsible drug in the early period of the reaction will reduce mortality and morbidity in these cases. As reported in the literature, mortality in DRESS syndrome is mainly secondary to hepatic failure. Liver transplantation cannot be effective due to systemic involvement and the risk of recurrence in the transplanted liver. For these reasons, liver transplantation in DRESS syndrome may not decrease mortality.[10]

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References

1. James J, Sammour YM, Virata AR, Nordin TA, Dumic I. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome secondary to furosemide: Case report and review of literature. Am J Case Rep 2018;19:163-170.
2. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al; RegiSCAR study group. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol 2013;169(5):1071-1080. [CrossRef]
3. De A, Rajagopalan M, Sarda A, Das S, Biswas P. Drug reaction with eosinophilia and systemic symptoms: An update and review of recent literature. Indian J Dermatol 2018;63(1):30-40. [CrossRef]
4. Gupta R, Bhatia J, Gupta SK. Risk of hepatotoxicity with add-on leflunomide in rheumatoid arthritis patients. Arzneimittelforschung 2011;61(5):312-316.
5. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part I. Clinical perspectives. J Am Acad Dermatol 2013;68:693.e1-14; quiz 706-708. [CrossRef]
6. Vaish AK, Tripathi AK, Gupta LK, Jain N, Agarwal A, Verma SK. An unusual case of DRESS syndrome due to leflunomide. BMJ Case Rep 2011;2011:bcr0620114330. [CrossRef]
7. Mennicke M, Zawodniak A, Keller M, Wilkens L, Yawalkar N, Stickel F, et al. Fulminant liver failure after vancomycin in a sulfasalazine-induced DRESS syndrome: fatal recurrence after liver transplantation. Am J Transplant 2009;9:2197-2202. [CrossRef]
8. Ichai P, Laurent-Bellue A, Saliba F, Moreau D, Besch C, Francoz C, et al. Acute liver failure/ınjury related to drug reaction with eosinophilia and systemic symptoms: Outcomes and prognostic factors. Transplantation 2017;101(8):1830-1837. [CrossRef]
9. Walsh S, Diaz-Cano S, Higgins E, Morris-Jones R, Bashir S, Bernal W, et al. Drug reaction with eosinophilia and systemic symptoms: is cutaneous phenotype a prognostic marker for outcome? A review of clinicopathological features of 27 cases. Br J Dermatol 2013;168(2):391-401. [CrossRef]
10. Lin IC, Yang HC, Strong C, Yang CW, Cho YT, Chen KL, et al. Liver injury in patients with DRESS: A clinical study of 72 cases. J Am Acad Dermatol 2015;72(6):984-991. [CrossRef]